American Journal of Medical Genetics 63:482–485 (1996)

Mosaic Tetrasomy 15q25→qter in a Newborn Infant With Multiple Anomalies

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We describe a premature boy with metopic craniosynostosis, facial anomalies, atrial-septal defect, hydronephrosis and flexion contractures of lower limbs, and mosaic tetrasomy 15q25→qter. The extra chromosome material was present in the form of an acentric marker. A number of clinical manifestations observed in this child were also found in 3 previously reported patients who were trisomic for the same part of chromosome 15 and in 2 patients who were tetrasomic for a larger segment of 15q.

KEY WORDS: tetrasomy 15q25→qter, chromosome 15, mosaicism, marker chromosome

INTRODUCTION

Tetrasomy is a rare finding in humans. The presence of 2 extra copies of a given chromosome region is most often the result of isochromosome formation. Examples are tetrasomy 5p [Stanley et al., 1993], 8p [Newton et al., 1993], 9p [Melaragno et al., 1992], 12p [Reynolds et al., 1989], and 18p [Takeda et al., 1989]. To our knowledge, tetrasomy 15q has been reported only in 2 other patients [Blennow et al., 1994]. Here we describe a patient with mosaic tetrasomy 15q25→qter due to the presence of a supernumerary acentric isochromosome.

CLINICAL REPORT

The propositus was the first child of a 22-year-old mother and 23-year-old father. The parents were non-consanguineous. Gestation was uneventful until spontaneous rupture of the membranes at 29 weeks. Ultrasound examination of the fetus showed bilateral hydronephrosis. The next day, a boy was born after a vaginal delivery in vertex position. Birth weight was 1,530 g (50th–90th centile), length 44 cm (>90th centile), and head circumference (OFC) 26.5 cm (10th–50th centile). Apgar scores were 3, 6, and 10 at 1, 5 and 10 minutes, respectively. There was intubation at 5 minutes because the child had no spontaneous respiration. On physical examination, several anomalies were noted. The skull was turricephalic with a metopic ridge. The face was characterized by blepharophimosis, high and broad nasal bridge, small mouth, and micrognatia. Bilateral cup-shaped ears were present (Fig. 1). Fingers and toes were long. The 5th finger was overriding the 4th bilaterally. The 2nd toe was overlapping the first and the 4th toe was overlapping the 5th. Flexion contractures of the lower limbs were also noted (Fig. 1). Echocardiogram showed a large atrial-septal defect with a considerable left-right shunt, as well as an open ductus arteriosus with a left-right shunt. The left kidney was 4.1 cm with hydronephrosis, the right kidney was 3.0 cm with some indication of hydronephrosis. Computed tomographic (CT) scan of the skull showed blood in the right ventricle and an impression of a metopic craniosynostosis. The boy remained ventilatory dependent and died at one month. An autopsy was not performed.

CYTOGENETIC INVESTIGATION

Cytogenetic analysis was performed on peripheral blood lymphocytes according to standard methods. An extra marker chromosome was found in 79% of cells. C-banding showed absence of centromeric heterochromatin. The high resolution GSW-banding pattern was suggestive of a chromosome 15 or 20 origin (Fig. 2). Fluorescence in situ hybridization (FISH) was performed according to van Roy et al. [1994]. Using chromosome 15 and 20 specific libraries [pBS-15, pBS-20; Collins et al., 1991], the marker chromosome was shown to be derived from a chromosome 15 (Fig. 3a). Subsequently, FISH was performed with p80, a 14 kb clone of the FES protooncogene, located at 15q25-qter [Heisterkamp et al., 1982]. This probe hybridized to both ends of the marker chromosome at equal distance of the center of the marker (Fig. 3b). According to cytogenetic and FISH results, the marker chromosome could be described as

Received for publication March 2, 1995; revision received October 20, 1995.

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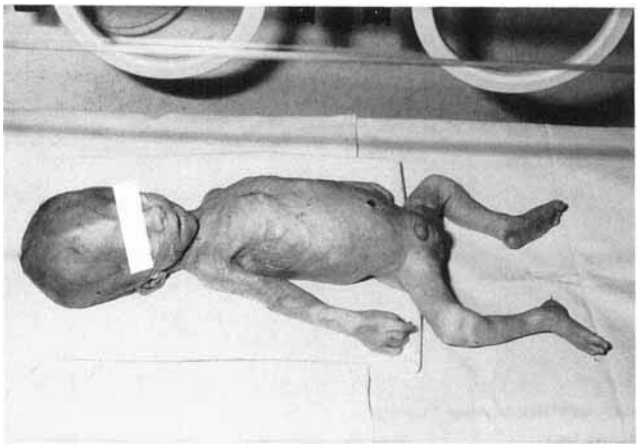

Fig. 1. Postmortem appearance of the patient.

an acentric isochromosome for the distal part of chromosome 15, resulting in the following karyotype 46,XY/47,XY,+ace i(15)(qter→q25::q25→qter) (Fig. 4). The chromosomes of the parents were normal.

DISCUSSION

We describe a patient with a mosaic tetrasomy 15q25→qter due to the presence of a supernumerary acentric isochromosome in 79% of his peripheral blood lymphocytes. To the best of our knowledge, this is the 3rd patient with tetrasomy 15q described in the literature. The breakpoints in the 2 patients with mosaic tetrasomy 15q described by Blennow et al. [1994] are located more proximally when compared to the marker found in our patient. Despite this difference, the clinical appearance is quite similar. Common findings are antimongoloid slant, apparently low-set ears, large nose, micro/retrognathia, long philtrum, down-turned corners of the mouth, asymmetry of the head, long fingers and toes, and joint contractures of the hips (Table I). Because our patient was a premature child and died after one month, mental retardation, sensorineural hearing loss, and increased postnatal growth could not be evaluated.

Trisomy for the 15q25→qter segment has been described in 3 patients [Pedersen, 1976; Kristofferson and Bergwall, 1984]. A number of traits noted in those patients such as low-set ears, large nose, asymmetry of the head, micro/retrognathia, long fingers and toes, were also observed in our patient (see Table I). Blennow et al. [1994] have pointed at the similarities between their patients with tetrasomy 15q and patients reported with trisomy of various segments of 15q.

In our patient, a number of manifestations were observed which have not been described earlier in patients with trisomy 15q25→qter or tetrasomy 15q25→qter. These include blepharophimosis, small mouth, cup-shaped ears, and hydronephrosis. Clearly more patients

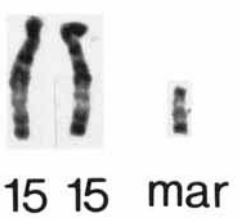

Fig. 2. Partial high resolution G-banded karyotype showing the normal chromosomes 15 and the marker chromosome.

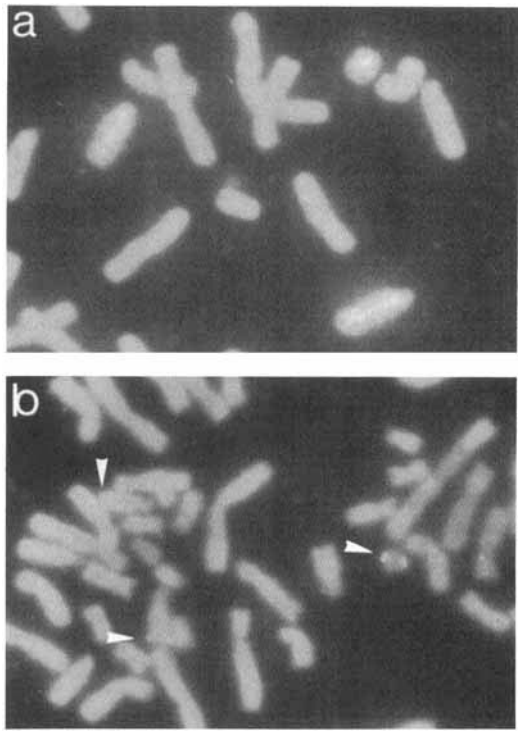

Fig. 3. Metaphase after hybridization with **(a)** a chromosome 15-specific library and **(b)** a probe for the FES protooncogene located at 15q25-qter (arrowheads in b point at the hybridization signals of FES).

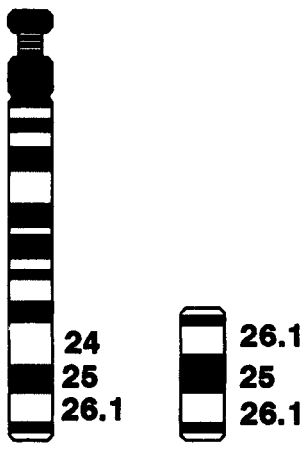

Fig. 4. Ideogram of chromosome 15 and the ace i(15)(qter→q25::q25→qter).

TABLE I. Clinical Features of the Present Case Compared With Those of Patients With Trisomy 15q25-qter, Tetrasomy 15q23-qter, and Trisomy 15q*

	Tetrasomy 15q			Trisomy 15q25-qter			
	Kristofferson and Bergwall [1984]		Pedersen [1976]	Blennow et al. [1994]		Present case	Trisomy 15q
	Case 1	Case 2		Case 1	Case 2		
Antimongoloid slant	–	–	+	+	+	–	+
Low-set ears	+	+	+	+	+	+	+
Bulbous nose	+	+	–	+	+	+	+
Nasal stenosis	–	–	–	+	–	–	–
Long philtrum	–	–	+	+	+	+	+
Down-turned corners of the mouth	–	–	+	+	+	–	+
Midline in lower lip	–	–	–	–	–	–	+
High-arched palate	+	+	+	+	+	?	+
Microretrognathia	+	+	–	+	+	+	+
Short neck	+	+	–	–	–	–	+
Asymmetry of the head	–	+	+	+	+	+	+
Sloping forehead	–	–	–	–	–	–	+
Asymmetry of the thorax	–	–	–	+	+	–	+
Kyphosis/scoliosis	–	–	–	+	+	–	+
Arachnodactyly	+	+	–	+	+	+	+
Genital anomalies	–	–	–	–	–	–	+
Cardiac defects	–	+	–	–	–	+	+
Joint defects	+	+	–	+	+	+	+
Achromatopsia	–	–	–	+	–	?	–
Sensorineural hearing loss	–	–	–	+	+	?	–
Mental retardation	+	+	+	+	+	?	+
Increased postnatal growth	+	+	–	+	+	–	–

* Adapted from Blennow et al. [1994].

need to be studied with tetrasomy 15q to establish the clinical picture of this chromosomal abnormality.

Using C-banding, no centromere-associated heterochromatin could be detected in the marker chromosome. Using FISH, the presence of alphoid DNA sequences could also be excluded. These observations may explain the presence of a normal cell line, as the absence of centromeric DNA sequences is likely to cause anaphase lag and subsequent nondisjunction. On the other hand, the marker chromosome was retained in a relatively high proportion of peripheral blood lymphocytes, suggesting a relatively stable transmission during metaphase. Other examples of molecular cytogenetically characterized C-negative and/or alphoid DNA-negative markers were published by Callen et al. [1992], Crolla et al. [1992], Rauch et al. [1992], Magnani et al. [1993], Voullaire et al. [1993], and Ohashi et al. [1994]. Only a few marker chromosomes have been studied in greater detail. The supernumerary marker analyzed by Ohashi et al. [1994] contained a functional kinetochore as demonstrated by anti-kinetochore staining using serum from CREST patients. Voullaire et al. [1993] described a mitotically stable marker chromosome with a primary constriction but without evidence of the presence of α-satellite, satellite III, or CENP-B protein. Without deeper insights into the molecular structure of the critical region for centromere function, we can only speculate on the mechanism of formation of these marker chromosomes and the reasons for their mitotic stability. Several hypotheses have been put forward including activation of intercalary ancient centromere sequences or complex rearrangements involving the centromeric region of the same or another chromosome.

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